DATE: **March 17, 1999**

MEMORANDUM

SUBJECT: **Phostebupirim (129086): Reassessment of Acute and Chronic RfDs**

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THROUGH: Alan Nielsen, Branch Senior Scientist
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1. Background: Bayer Corporation submitted acute (MRID: 43473001) and subchronic (MRID: 43656302) neurotoxicity studies in the rat, but were not reviewed prior to the Comprehensive Review of the Organophosphates meeting on May 12, 13, and 14, 1998. Because these studies were not available at the time of the meeting, the requirements for the acute and subchronic neurotoxicity studies in the rat were viewed as data gaps. As a result of the data gaps, an FQPA Safety Factor of a 3X was retained. The current endpoints and doses used for acute and chronic risk assessments are summarized in Table 1.

Table 1: Current Endpoints and Doses for Use in Acute and Chronic Risk Assessment

	Acute	Chronic
Critical Study	Developmental Rabbit Study (MRID 42005455 and 42981901)	1-Year Dog Feeding Study (MRID 42005452 and 42119301)
Endpoint	Plasma and RBC ChEI [a] at gestation day 14	Plasma, RBC and brain ChEI
NOAEL	0.1 mg/kg/day	0.02 mg/kg/day
UF	UF=100 10X inter- and 10X intraspecies variation	UF=100 10X inter- and 10X intraspecies variation
RfD	0.001 mg/kg/day	0.0002 mg/kg/day
FQPA Safety Factor	Reduced to 3X	Reduced to 3X
PAD [b]	**0.0003 mg/kg/day**	**0.00007 mg/kg/day**

a ChEI = Cholinesterase Inhibition

b PAD = Population Adjusted Dose $= \frac{\text{Acute or Chronic RfD}}{\text{FQPA Safety Factor}}$

2. Results of Neurotoxicity Studies: The acute and subchronic neurotoxicity studies in the rat were reviewed and found to be acceptable. The guideline requirements, §81-8 and §82-5(b), have been satisfied. The results of these studies are briefly summarized in Table 2.

Table 2: Results of Acute and Subchronic Neurotoxicity Studies in the Rat

	Acute Neurotoxicity Study	Subchronic Neurotoxicity Study
Doses Tested	Male: 0, 0.5, 1.0, 5.0 mg/kg Female: 0, 0.25, 0.5, 1.0 mg/kg	Male: 0, 0.26,1.2 and 4.4 mg/kg/day Female: 0, 0.30, 0.96, and 3.6 mg/kg/day
NOAEL	Males: Not established Females: 0.25 mg/kg	Not established
LOAEL	Males: 0.5 mg/kg Females: 0.5 mg/kg	Males: 0.26 mg/kg/day Females: 0.30 mg/kg/day
Basis for LOAEL	% ChEI Plasma / RBC / Brain Males 26* / 20* / 3 (ns) Females 31* / 32* / 9 (ns) At 1.5 hr post-dosing	% ChEI Day / Plasma / RBC / Brain Male 24 / 5 (ns) / 66* / --- Female 25 / 26* / 69* / --- Male 87 / 40* / 66* / 7* Female 88 / 27* / 72* / 13*

a ChEI = Cholinesterase Inhibition, * $p \leq 0.05$ vs control, ns = not significant, --- Not measured

3. Recommendation to the HIARC: Since Bayer Corporation has satisfied the requirements

for acute and subchronic neurotoxicity studies in the rat, the 3X FQPA safety factor should be removed. It is further recommended that the acute neurotoxicity study in the rat be used to establish the acute dietary risk assessment. The acute (single dose) study is a more realistic exposure scenario than the developmental study in the rabbit, which showed effects (plasma and RBC ChEI) only after nine doses. Based on these findings, the following endpoints and doses for acute and chronic risk assessment are recommended to the committee:

Table 3: Proposed Doses and Endpoints for Acute and Chronic Dietary Risk Assessment

	Acute	**Chronic**
Critical Study	Acute Neurotoxicity Study in the Rat (MRID 43473001)	1-Year Dog Feeding Study (MRID 42005452 and 42119301)
Endpoint	Plasma and RBC ChEI [a] at 1.5 hr post-dosing	Plasma, RBC and brain ChEI
NOAEL	0.5 mg/kg (LOAEL) NOAEL not achieved in males	0.02 mg/kg/day
Uncertainty Factor	UF= 300 100X inter- and intraspecies variation and 3X lack of NOAEL	UF=100 100X inter- and intraspecies variation
RfD	**0.002 mg/kg**	**0.0002 mg/kg/day**
FQPA Safety Factor	**1 (FQPA factor removed)**	**1 (FQPA factor removed)**
PAD [b]	**0.002 mg/kg** (Same as acute RfD)	**0.0002 mg/kg/day** (Same as chronic RfD)

a ChEI = Cholinesterase Inhibition

b PAD = Population Adjusted Dose $= \frac{\text{Acute or Chronic RfD}}{\text{FQPA Safety Factor}}$

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